Pulm Ther
https://doi.org/10.1007/s41030-024-00255-1

ORIGINAL RESEARCH

Association between Increased Risk of Pneumonia with ICS in COPD: A Continuous Variable Analysis of Patient Factors from the IMPACT Study

Bhumika Aggarwal · Paul Jones · Alejandro Casas · Mauro Gomes · Siwasak Juthong · Diego Litewka · Bernice Ong-Dela Cruz · Alejandra Ramirez-Venegas · Abdullah Sayiner · James van Hasselt · Chris Compton · Lee Tombs · Stephen Weng · Gur Levy

Received: January 11, 2024 / Accepted: February 8, 2024

ABSTRACT

Introduction: Despite the proven benefits of inhaled corticosteroid (ICS)-containing triple therapy for chronic obstructive pulmonary disease (COPD), clinicians limit patient exposure to ICS due to the risk of pneumonia. However, there are multiple factors associated with the risk of pneumonia in patients with COPD. This post hoc analysis of IMPACT trial data aims to set the risks associated with ICS into a context of specific patient-related factors that contribute to the risk of pneumonia.

Methods: The 52-week, double-blind IMPACT trial randomized patients with symptomatic COPD and ≥1 exacerbation in the prior year 2:2:1 to once-daily fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI), FF/VI or UMEC/VI. Annual rate of on-treatment pneumonias in the intent-to-treat population associated with age, body mass index (BMI), percent predicted forced expiratory volume in 1 s (FEV_1)

B. Aggarwal (✉)
Emerging Markets, GSK, 23 Rochester Park, Singapore 139234, Singapore
e-mail: bhumika.x.aggarwal@gsk.com

P. Jones
Global Medical, Regulatory and Quality, GlaxoSmithKline Plc., Brentford, UK
e-mail: paul.8.jones@gsk.com

A. Casas
AIREPOC (Integrated Care and Rehabilitation Program of COPD), Pulmonary Colombian Foundation, and El Rosario University, Bogotá, Colombia
e-mail: acasac@neumologica.org

M. Gomes
Department of Pneumology at Santa Casa Medical School, São Paulo, Brazil

M. Gomes
Hospital Samaritano-Higienopolis, São Paulo, Brazil
e-mail: gomesm@uol.com.br

S. Juthong
Division of Respiratory and Respiratory Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand
e-mail: jsiwasakmd@gmail.com

D. Litewka
Unidad Neumonologia, Hospital Juan A. Fernandez, Buenos Aires, Argentina
e-mail: litedie@gmail.com

B. Ong-Dela Cruz
Division of Pulmonary and Critical Care Medicine, Philippine Heart Center, Quezon, Philippines
e-mail: berns_ong@yahoo.com

A. Ramirez-Venegas
Department of Research in Tobacco and COPD, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
e-mail: aleraves@gmail.com

Published online: 06 March 2024

and blood eosinophil count (BEC) was evaluated.

Results: This analysis revealed that the annual rate of pneumonia showed the lowest risk at the age of 50 years. The 95% confidence intervals (CI) between ICS-containing and non-ICS containing treatments diverged in ages > 63 years, suggesting a significantly increased ICS-related risk in older patients. In contrast, the annual rate of pneumonia rose in both groups below BMI of 22.5 kg/m^2, but above that, there was no relationship to pneumonia rate and no differential effect between the two groups. The relationship between BEC and pneumonia was flat up to > 300/μL cells with ICS-containing treatment and then rose. In contrast, the rate of pneumonia with non-ICS containing treatment appeared to increase at a lower level of BEC (~ 200/μL).

Conclusions: There was little evidence of a differential effect of older age, lower BMI, lower FEV_1 and BEC on the pneumonia rate between ICS-containing and non-ICS containing treatments. This analysis points to the need for a balanced approach to risk versus benefit in the use of ICS-containing treatments in COPD.

Clinical trial registration: IMPACT ClinicalTrials.gov number, NCT02164513.

A. Sayiner
Department of Chest Diseases, Ege University Faculty of Medicine, Izmir, Turkey
e-mail: sayiner2011@gmail.com

J. van Hasselt
GSK, Regional Medical Affairs, Bryanston, Gauteng, South Africa
e-mail: james.d.van-hasselt@gsk.com

C. Compton · S. Weng
GSK, Brentford, UK

C. Compton
e-mail: chris.h.compton@gsk.com

S. Weng
e-mail: stephen.f.weng@gsk.com

L. Tombs
Precise Approach Ltd, London, UK
e-mail: lee.x.tombs@gsk.com

G. Levy
Emerging Markets, GSK, Panama City, Panama
e-mail: gur.y.levy@gsk.com

Keywords: IMPACT; Post hoc analysis; Pneumonia risk; COPD; ICS

Key Summary Points

Why carry out the study?

Multiple factors contribute to the elevated pneumonia risk in patients with COPD.

ICS-containing triple therapy improves outcomes in patients with COPD but raises concerns of pneumonia risk.

This post hoc analysis analysed the impact of factors such as patient's age, BMI, FEV_1 and blood eosinophil counts on the pneumonia risk in patients treated with triple therapy in the phase 3 IMPACT trial.

What was learned from the study?

Older age, lower BMI and lower FEV_1 were associated with increased pneumonia risk, however, blood eosinophil count did not have an impact on the pneumonia risk in patients receiving triple therapy.

There is a need for a balanced clinical approach of risk versus benefit in the use of ICS-containing treatments in COPD.

INTRODUCTION

Risk of pneumonia remains a concern despite the well-defined benefits of treating appropriate patients with chronic obstructive pulmonary disease (COPD) using inhaled corticosteroid (ICS)-containing therapies. Several studies have documented an incidence of pneumonia between 2% and 8% in patients with COPD receiving ICS-containing triple therapy [1–3]. Previous studies have shown that multiple patient factors can potentially increase the risk of developing pneumonia. These include advanced age, lower body mass index (BMI), worse lung function, presence of asthma along with COPD, previous history of pneumonia

and/or exacerbations and smoking status [3, 4]. Williams et al. in 2017 identified various predictors of pneumonia in patients with COPD over 5 years of follow-up, including more severe disease, gender and ICS use [4]. A post hoc analysis of the TORCH trial identified advanced age, low BMI and low forced expiratory volume in 1 s (FEV_1), along with previous exacerbation history, to be contributing factors for the elevated risk of developing pneumonia in patients with COPD receiving ICS-containing therapy [5]. A pooled individual patient data analysis of five clinical trials reported similar observations, in addition to ICS-containing therapy, low BMI, previous history of exacerbations, worsening lung function and more severe lung disease as pneumonia risk factors [6]. However, these trials varied in size and duration, and none included ICS as a component of triple therapy. This analysis was thus performed using data from a single large study, the IMPACT trial, of more than 10,000 patients known to be at significant risk of exacerbations.

METHODS

A post hoc analysis was conducted utilizing the data from the IMPACT study to assess the association between the annual rate of pneumonia and demographic factors, analysed as continuous variables, including age, BMI, FEV_1 and blood eosinophil count (BEC).

Study Design

The IMPACT study (GSK study CTT116855; NCT02164513) was a phase 3, 52-week, randomized, double-blind, parallel-group, multicentre study comparing single-inhaler triple therapy with fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (FF/UMEC/VI) with once-daily dual therapy with FF/VI or UMEC/VI dual therapy. Patients were randomized (2:2:1) to receive FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg or UMEC/VI 62.5/25 mcg, all administered once daily via the ELLIPTA dry-powder inhaler. The study design and primary results have been previously published [3].

Study Population

Inclusion and exclusion criteria have been described previously [3]. Briefly, eligible patients were $\geq$ 40 years of age with symptomatic COPD [COPD Assessment Test (CAT) score $\geq$ 10 at screening], and either a $FEV_1 <$ 50% of predicted normal values and $\geq$ 1 moderate or severe exacerbation in the previous year, or FEV_1 50% to $<$ 80% of predicted normal values and $\geq$ 2 moderate or $\geq$ 1 severe exacerbation in the previous year. Patients with significant bronchiectasis were excluded. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and received approval from local institutional review boards or independent ethics committees. All patients in that study provided written informed consent.

Endpoints

This post hoc analysis evaluated the annual rate of on-treatment pneumonias in the intent-to-treat (ITT) population for each of the following baseline characteristics that could be analysed as a continuous variable: age, BMI, FEV_1% predicted and BEC.

Statistical Analyses

Fractional polynomials (FP) were used to model the relationship between the baseline characteristic of interest as a continuous variable and the treatment outcomes. This method preserves the continuous nature of the covariates in a regression model and allows nonlinear associations to be tested. The selected best fitting model was plotted as the baseline characteristic versus the annual rate of on-treatment pneumonias in each treatment group. The covariates included in each of the models mirror those included in the analysis of the primary endpoint (moderate plus severe exacerbations) in the primary study and were defined a priori. We used modelling of continuous variables of age, BMI, FEV_1 and BEC by treatment group in IMPACT (FF/UMEC/VI, FF/VI, UMEC/VI) to evaluate the annual rate of pneumonia. Models

were fitted by using the continuous variables as FPs in negative binomial models with covariates of treatment group, geographical region, age, BMI, smoking status (screening), sex, pneumonia history, BEC, FP1, FP2, FP1*treatment and FP2*treatment. FP1 and FP2 represent continuous transformations of the variables of interest (i.e. age, BMI, FEV_1, BEC) in each respective model.

RESULTS

Of the 10,355 patients randomly assigned in the ITT population, pneumonia was reported in 184 (4%), 152 (4%) and 54 (3%) patients in the FF/UMEC/VI, FF/VI and UMEC/VI arms, respectively. The rate [number of events] of pneumonia in the FF/UMEC/VI, FF/VI and UMEC/VI arms was 53.3 [198], 47.7 [165] and 32.4 [55], respectively.

The incidence of pneumonia was evaluated using the long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA) arm as a baseline control, and the results show a 1.6-fold higher rate (Table 1). Data for pneumonia serious adverse events (SAEs) showed a 1.7-fold difference versus LAMA/LABA (Table 1).

Amongst these factors, those that could be analysed as a continuous variable were selected in addition to BEC to better understand their relationship to increased pneumonia risk.

Table 1 Pneumonia incidence in the IMPACT study

	IMPACT study
Study arms	1. FF/UMEC/VI QD (N = 4151)
	2. FF/VI QD (N = 4134)
	3. UMEC/VI QD (N = 2070)
Pneumonia AE	7.6% versus 7.1% versus 4.7%[#]
Pneumonia AE incidence in ICS-containing versus non-ICS treatment arms	Fold difference
	1 versus 3: 1.6-fold
	2 versus 3: 1.5-fold
Pneumonia SAE	4.4% versus 3.7% versus 2.6%
Pneumonia SAE incidence in ICS-containing versus non-ICS treatment arms	Fold difference
	1 versus 3: 1.7-fold
	2 versus 3: 1.4-fold

[#]Reported as pneumonia AESI

AE adverse event; *AESI* adverse event of special interest; *FF* flut icasone furoate; *ICS* inhaled corticosteroid; *QD* quaque die or once a day; *SAE* serious adverse event; *UMEC* umeclidinium; *VI* vilanterol

Association with Age

The annual rate of pneumonia began to rise above the age of 50 years. The rate was higher in the ICS-containing treatment arms compared with the non-ICS containing arm, and this difference increased with age (Fig. 1).

Association with BMI

When fitted against BMI of the patients, the annual rate of pneumonia was found to be higher in patients with a lower BMI and this effect was most pronounced with the FF/VI cohort. The pneumonia risk for the three treatment arms (FF/UMEC/VI, FF/VI and UMEC/VI) increased in patients with BMI < 22.5 kg/m^2 and the risk appeared to level out for all treatment cohorts in patients with BMI > 22.5 (Fig. 2).

Association with Lung Function

When the annual pneumonia rate was fitted against lung function, as noted by a lower FEV_1, it was observed that worse lung function at the initiation of ICS containing triple therapy is associated with higher risk of developing pneumonia in patients with COPD (Fig. 3).

Association with Blood Eosinophils

The relationship between BEC and pneumonia was flat up to $> 300/\mu$L cells with both ICS-containing treatments and then increased. In

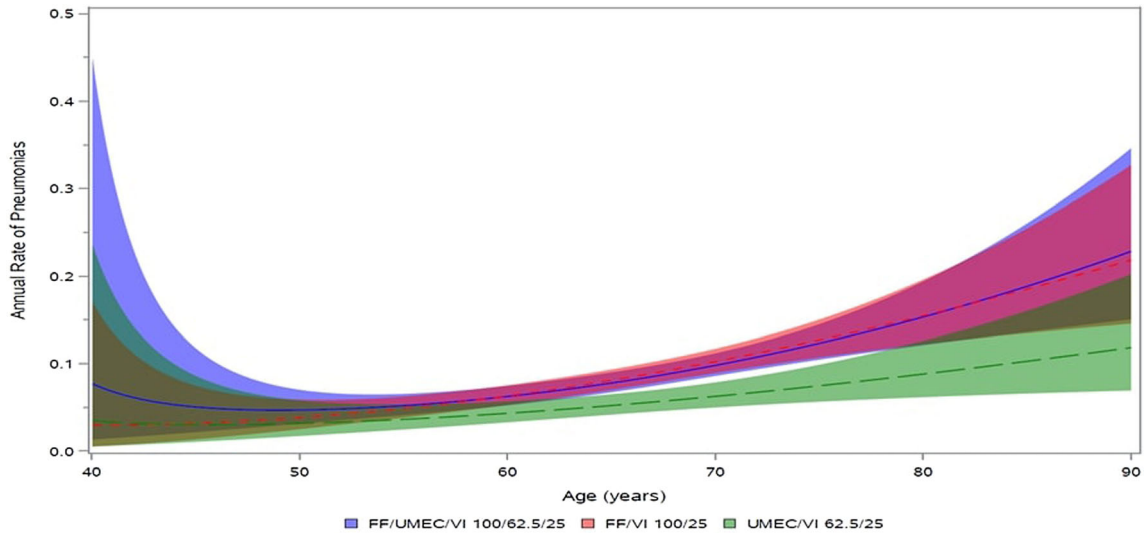

Fig. 1 Annual rates of pneumonia risk by patient age among different treatments (FF/UMEC/VI versus UMEC/VI versus FF/VI). *FF* fluticasone furoate; *UMEC* umeclidinium; *VI* vilanterol

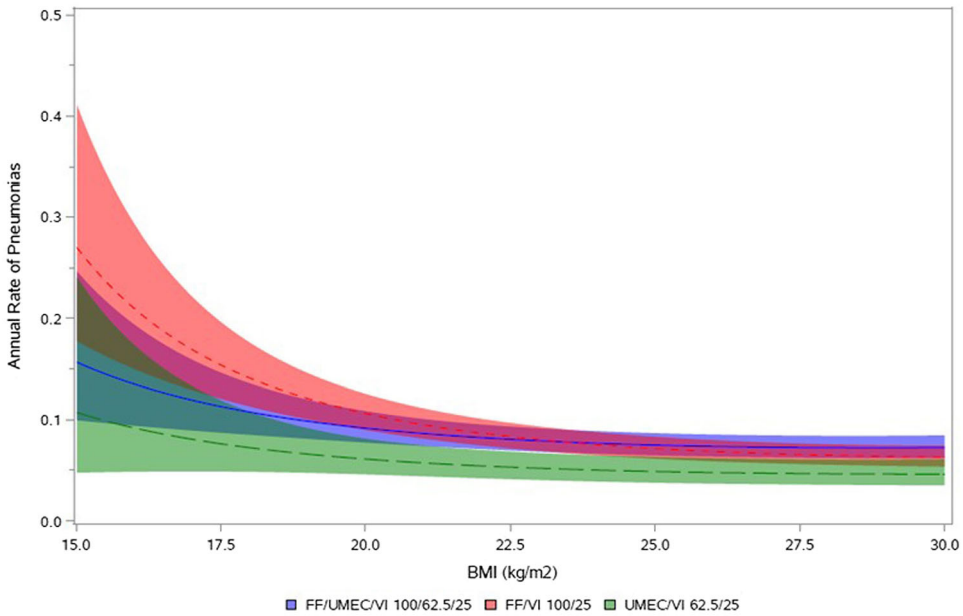

Fig. 2 Annual rates of pneumonia risk by BMI among different treatments (FF/UMEC/VI versus UMEC/VI versus FF/VI). *BMI* body mass index; *FF* fluticasone furoate; *UMEC* umeclidinium; *VI* vilanterol

contrast, the rate of pneumonia in the non-ICS containing arm appeared to increase at a lower level of BEC (~ 200/μL) (Fig. 4).

DISCUSSION

This post hoc analysis of the annual rate of pneumonia data from the 52-week IMPACT trial confirms the effect of different patient factors on pneumonia risk in COPD and extends them with data on blood eosinophils. This risk was

seen irrespective of the ICS-containing or non-ICS containing treatment regimen but was higher in those patients receiving an ICS-containing regimen.

Across all variables assessed in this study, annual rate of pneumonia in patients on ICS-containing triple therapy was lower in case of lower age group patients, in patients with higher BMI and in those with less decline in FEV_1. The pneumonia risk was seen to be the least with the cohort receiving UMEC/VI, though similar effects of age, BMI and lung function were still applicable. It is noteworthy that the absolute annual rate of pneumonia was small in all the three treatment cohorts, including the ICS-containing triple therapy cohort.

Overall, the pneumonia rate in the triple therapy arm was 7.6%, compared with 4.7% in the non-ICS arm, and the upper 95% CI for the rate of pneumonia in patients on ICS-containing triple therapy crossed 10% in patients aged > 67 years, BMI < 20, FEV_1 < 45% predicted and BEC > 300/μL. It has been established through evidence from multiple studies that there are many factors beyond ICS use that increase the risk of pneumonia in patients receiving treatment for COPD. The factors that may result in higher odds of developing pneumonia include more severe disease (GOLD stage IV versus GOLD stage I), followed by previous history of pneumonia, BMI and age of the patients, amongst others [4, 5, 7–10]. The most important new observation from this analysis is the absence of any relationship between pneumonia and BEC < 300/μL with no differential effect of ICS-containing versus non-ICS containing treatment. However, the rate of pneumonia with non-ICS containing treatment appeared to increase at a lower level of BEC (~ 200/μL). A previous meta-analysis of ten studies suggested that, overall, there may be an increased risk of pneumonia in patients with BEC > 2%. However, in patients treated with ICS, pneumonia occurred in 4.5% of patients with BEC < 2% and 3.9% of patients with BEC ≥ 2%. Those authors concluded that the magnitude of the increased risk was small and should be further explored in large prospective studies [11].

IMPACT was a large prospective study, and the great majority of the patients' BEC lay in the range of < 300/μL cells, so confidence can be placed in this observation. One study reported

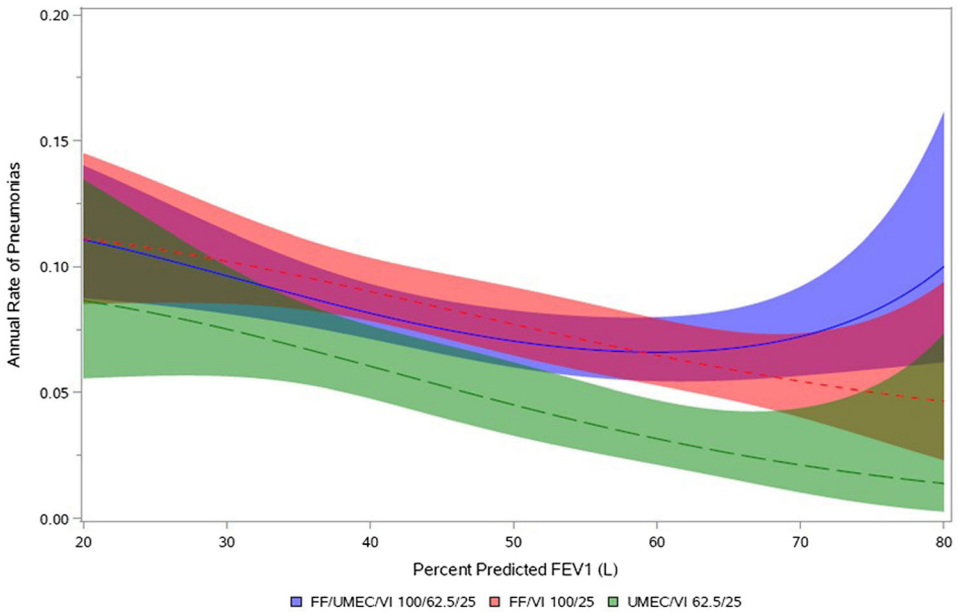

Fig. 3 Annual rates of pneumonia risk by lung function among different treatments (FF/UMEC/VI versus UMEC/VI versus FF/VI). *FEV1* forced expiratory volume in 1 second; *FF* fluticasone furoate; *UMEC* umeclidinium; *VI* vilanterol

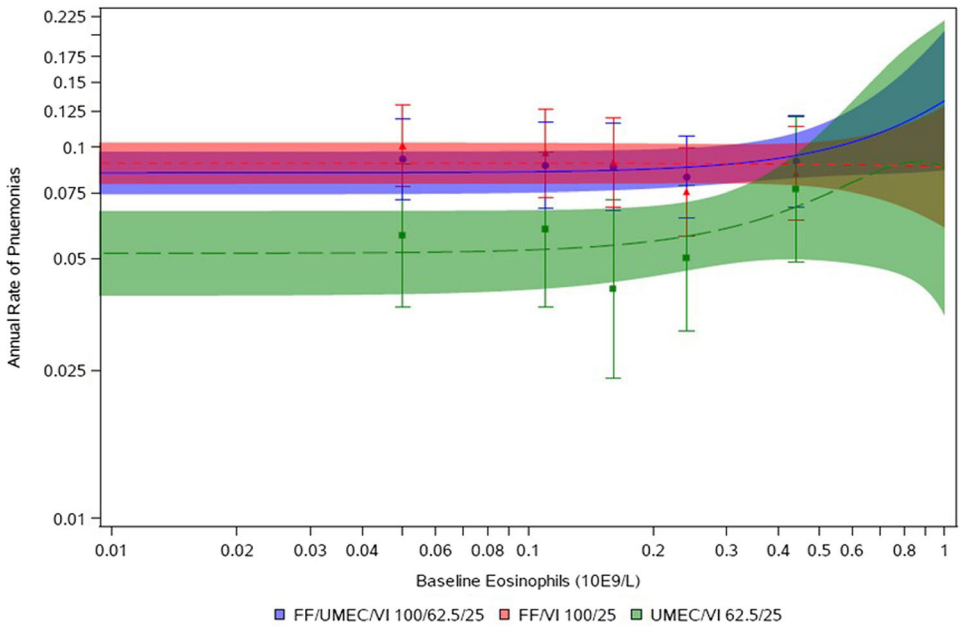

Fig. 4 Annual rates of pneumonia risk by BEC among different treatments (FF/UMEC/VI versus UMEC/VI versus FF/VI). *BEC* Blood eosinophil count; *FF* fluticasone furoate; *UMEC* umeclidinium; *VI* vilanterol

that patients with chronic bronchial infection and BEC < 100 cells/μL were at increased risk of pneumonia but constituted 21% of the study population (42 patients) [12]. Whilst our findings do not refute those observations, the absence of any trend for increased pneumonia risk in this large population of patients at high risk of exacerbation suggests any increased risk is confined to that specific group of patients.

We do not have an adequate explanation for the increased rate of pneumonia in patients with very high BEC. This seems to be a real phenomenon, seen in all three treatment arms. One plausible explanation may be the misdiagnosis of an episode of eosinophilic pneumonia in patients who also have COPD. This is a T-helper 2 cell-mediated disease, so the fact that the increase in pneumonia rate was seen most clearly in patients who are not on ICS provides some support for this suggestion [13]. Our findings have important implications for the use of ICS-containing triple therapy. Since all treatments should be used in the context of risk versus benefit, whilst it is clear that at a population level, the probability of benefit with ICS to reduce exacerbations is lower in patients with lower BEC, this is not accompanied by increased risk. In this context, it is paradoxical and unfortunate that the patients who are at greater risk of an exacerbation, specifically older patients [14], those with lower FEV_1 [15] or those with lower BMI [16], also have a greater risk of pneumonia. Risk and benefit are also important when considering ICS-containing treatment for patients at lower risk of exacerbations and earlier in their disease. Such patients are at lower risk of pneumonia by virtue of their age and lung function and are less likely to have emphysema-related loss of BMI. Thus, whilst they may have smaller benefits in terms of exacerbation reduction, they also have a lower risk of pneumonia. This consideration lends support to the design of studies testing triple therapies in younger and milder patients with COPD in an attempt to alter disease progression [17]. Therefore, the potential pneumonia risk needs to be balanced against potential benefits across a range of patient outcomes at the individual patient level [18–20]. The strengths of this analysis of the IMPACT study include the large sample size (N = 10,355) and the long duration of the study (52 weeks), which allowed for increased precision in the analysis of trends of patient factors

that contribute to the risk of pneumonia in COPD. However, it should be noted that these analyses are descriptive and were conducted post hoc.

In addition to age, BMI, COPD severity and BEC levels, there are several factors that may elevate the risk of pneumonia in patients with COPD. One of the limitations of the current analysis was that it did not assess other known factors implicated in potentially increasing the risk of pneumonia in patients with COPD, including smoking, oral corticosteroid use, history of exacerbations, dosage levels of ICS and presence of comorbidities such as cardiovascular diseases, asthma and bronchiectasis. These factors, and their association with pneumonia and ICS use, should be evaluated in future research.

CONCLUSIONS

The increasing annual rate of pneumonia was associated with older age, lower BMI and lower FEV_1. The key new observation in this study is the absence of any relationship between blood eosinophils and ICS-associated pneumonia risk. It seems clear that lower benefit versus risk in patients with lower eosinophils is due to lower potential benefit, not increased risk. Paradoxically, the patients at greatest risk of pneumonia are those who may have the greatest need for ICS-containing treatment to reduce the risk of exacerbations. These observations provide clinicians with additional insights to guide decisions concerning ICS-containing treatment for COPD at the individual patient level.

Medical Writing and Editorial Assistance. EVERSANA provided medical writing and editorial support; Costello Medical, UK provided publication coordination and was funded by GSK.

Author contributions. Bhumika Aggarwal was responsible for conceptualisation, data curation, formal analysis, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft and writing – review and editing; Paul Jones for conceptualisation, data curation, formal analysis, methodology, supervision, validation, visualisation and writing– review and editing; Alejandro Cassas for methodology, validation, visualisation, writing – original draft and writing – review and editing; Mauro Gomes for methodology, validation, visualisation, writing – original draft and writing – review and editing; Siwasak Juthong for methodology, validation, visualisation, writing – original draft and writing – review and editing; Diego Litewka for methodology, validation, visualisation, writing – original draft and writing – review and editing; Bernice Ong-Dela Cruz for methodology, validation, visualisation, writing – original draft and writing – review and editing; Alejandra Ramirez-Venegas for methodology, validation, visualisation, writing – original draft and writing – review and editing; Abdullah Sayiner for methodology, validation, visualisation, writing – original draft and writing – review and editing; James van Hasselt for conceptualisation, data curation, formal analysis, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft and writing – review and editing; Chris Compton for conceptualisation, data curation, formal analysis, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft and writing – review and editing; Lee Tombs for conceptualisation, data curation, formal analysis, methodology, supervision, validation, visualisation, writing – original draft and writing – review and editing; Stephen Weng for conceptualisation, data curation, formal analysis, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft and writing – review and editing; and Gur Levy for conceptualisation, data curation, formal analysis, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft and writing – review and editing.

Funding. This work and all costs associated with the publication were funded by GSK. The study sponsor also funded the journals' Rapid Service fee.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Bhumika Aggarwal is an employee of GSK and holds shares in GSK. Paul Jones is an employee of GSK and holds shares in GSK. Alejandro Casas has received payment for lectures, presentations, speaker's bureaus, manuscript writing or educational events from GSK (Colombia, Chile, and Global), AstraZeneca (Colombia and LATAM), and Boehringer Ingelheim (Colombia and Ecuador); has received support for attending a Colombian National Congress and scientific meetings from GSK Colombia; and has received payment for participation on a Data Safety Monitoring Board or Advisory Board from GSK Colombia. Mauro Gomes has not received payments for the present manuscript; has received payment for class presentation from Boehringer-Ingelheim, Chiesi and GSK; and has received support for registration for the European Congress ERS 2023 from Chiesi. Siwasak Juthong has no conflicts of interest to disclose. Diego Litewka has received payments from GSK for conferences and advisory boards. Bernice Ong-Dela Cruz has received honoraria and advisory board fees from GSK, AstraZeneca, Boehringer Ingelheim, Orient Euro Pharma (OEP) and Pfizer; and receives honoraria from United American Pharmaceuticals (UAP). Alejandra Ramirez-Venegas has received honoraria for speaking engagements from GSK and AstraZeneca. Abdullah Sayiner has received honoraria for serving on advisory boards and for speaking at meetings sponsored by GSK, Chiesi and Abdi Ibrahim. James van Hasselt is an employee of GSK and holds shares in GSK. Chris Compton is an employee of GSK and holds shares in GSK. Lee Tombs is a contractor for Veramed and a director for Precise Approach Ltd, London; he was contracted by GSK to conduct the statistical analysis for this study but received no payment for manuscript development. Stephen Weng is an employee of GSK and holds shares in GSK. Gur Levy is an employee of GSK and holds shares in GSK.

Ethical Approval. The present article is based on existing data from the phase 3 IMPACT trial and does not contain any new interventional studies with human participants or animal subjects performed by any of the authors. The IMPACT study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and received approval from local institutional review boards or independent ethics committees.

REFERENCES

1. Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;196(4):438–46. https://doi.org/10.1164/rccm.201703-0449OC.

2. Halpin DMG, Worsley S, Ismaila AS, et al. INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. ERJ Open Res. 2021;7(2):00950–2020. https://doi.org/10.1183/23120541.00950-2020.

3. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378(18):1671–80. https://doi.org/10.1056/NEJMoa1713901.

4. Williams NP, Coombs NA, Johnson MJ, et al. Seasonality, risk factors and burden of community-acquired pneumonia in COPD patients: a population database study using linked health care records. Int J Chronic Obstruct Pulmon Dis. 2017;12:313–22. https://doi.org/10.2147/COPD.S121389.

5. Crim C, Calverley PMA, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J 34:641–647. https://doi.org/10.1183/09031936.00193908.

6. Hartley BF, Barnes NC, Lettis S, Compton CH, Papi A, Jones P. Risk factors for exacerbations and pneumonia in patients with chronic obstructive pulmonary disease: a pooled analysis. Respir Res. 2020;21(1):5. https://doi.org/10.1186/s12931-019-1262-0.

7. Crim C, Dransfield MT, Bourbeau J, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. Ann Am Thorac Soc. 2015;12(1):27–34. https://doi.org/10.1513/AnnalsATS.201409-413OC.

8. Müllerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012;106(8):1124–33. https://doi.org/10.1016/j.rmed.2012.04.008.

9. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J. 2006;28(2):346–51. https://doi.org/10.1183/09031936.06.00131905.

10. Lin SH, Ji BC, Shih YM, et al. Comorbid pulmonary disease and risk of community-acquired pneumonia in COPD patients. Int J Tuberc Lung Dis. 2013;17(12):1638–44. https://doi.org/10.5588/ijtld.13.0330.

11. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. Lancet Respir Med. 2016;4(9):731–41. https://doi.org/10.1016/S2213-2600(16)30148-5.

12. Martinez-Garcia MA, Faner R, Oscullo G, et al. Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease. A network analysis. Am J Respir Crit Care Med. 2020;201(9):1078–85. https://doi.org/10.1164/rccm.201908-1550OC.

13. Singh R, Alape D, de Lima A, Ascanio J, Majid A, Gangadharan SP. Regulatory T cells in respiratory health and diseases. Pulm Med. 2019;20(2019):1907807. https://doi.org/10.1155/2019/1907807.

14. Müllerova H, Maselli DJ, Locantore N, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest. 2015;147(4):999–1007. https://doi.org/10.1378/chest.14-0655.

15. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128–38. https://doi.org/10.1056/NEJMoa0909883.

16. Adibi A, Sin DD, Safari A, et al. The acute COPD exacerbation prediction tool (ACCEPT): a modelling study. Lancet Respir Med. 2020;8(10):1013–21. https://doi.org/10.1016/S2213-2600(19)30397-2.

17. Singh D, Litewka D, Páramo R, et al. DElaying disease progression in COPD with early initiation of dual bronchodilator or triple inhaled pharmacotherapy (DEPICT): a predictive modelling approach. Adv Ther. 2023;40(10):4282–97. https://doi.org/10.1007/s12325-023-02583-1.

18. Bourbeau J, Bafadhel M, Barnes NC, et al. Benefit/risk profile of single-inhaler triple therapy in COPD. Int J Chronic Obstruct Pulmon Dis. 2021;1(16):499–517. https://doi.org/10.2147/COPD.S291967.

19. Miravitlles M, Acharya S, Aggarwal B, et al. Clinical concepts for triple therapy use in patients with COPD: a Delphi consensus. Int J Chronic Obstruct Pulmon Dis. 2023;28(18):1853–66. https://doi.org/10.2147/COPD.S424128.

20. Anzueto A, Cohen M, Echazarreta AL, et al. Delphi consensus on clinical applications of GOLD 2023 recommendations in COPD management: how aligned are recommendations with clinical practice? Pulm Ther. 2023. https://doi.org/10.1007/s41030-023-00248-6.